Trilostane in dogs

Sieber-Ruckstuhl, N S

• Clinic for Small Animal Internal Medicine, Vetsuisse Faculty,
University of Zürich

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N. Sieber-Ruckstuhl

Trilostane

Trilostane is a synthetic steroid analogue that inhibits the enzyme 3β-hydroxysteroid dehydrogenase (3β-HSD). The 3β-HSD is essential for the biosynthesis of all classes of steroid hormones, namely glucocorticoids, mineralocorticoids, progesterone, androgens and estrogens. Trilostane (Vetoryl®) is approved for treatment of canine hyperadrenocorticism (HAC).

1. Starting dose and frequency

When trilostane was introduced on the veterinary market the recommended staring dose was 2-10 mg/kg once daily. Nowadays, however, frequent users agree on much lower doses. We recommend a starting dose of 1-2 mg/kg once daily. Larger dogs (> 15 kg) need lower doses and should therefore be started on 1 mg/kg once daily.[1]

It is well known that the effect of trilostane does not last for 24h. Whether once- or twice-daily administration is better is unclear. We usually start dogs on once daily therapy. After 10-12 weeks we evaluate the dogs with a special focus on the clinical signs during the late afternoon and at night. If the suspicion arises that the effect of trilostane is too short, an ACTH stimulation test 24h after the last dosing is

performed. If the test confirms that activity is too short, the dog is changed to twice daily therapy. Dogs with concurrent diseases influenced by high cortisol levels (e.g. diabetes mellitus) as well as cats are started on 0.5-1 mg/kg twice daily.

Trilostane absorption is increased by food. Therefore, we tell our owners to administer trilostane with food.

2. Timing of dose adjustments

Regardless of the starting dose, dose adjustments, either up or down, will be required during the course of treatment.[2-4] The first recheck should be approximately after 10-14 days. However, the dose should only be changed if either the post-ACTH cortisol concentration is below ideal or if no clinical improvement has been noted and the post-ACTH cortisol concentration is still much higher than ideal. Cortisol concentrations decrease until 4 weeks after treatment start, even if the dog remains on the same dose. Further rechecks are recommended after about 4, 8, 12 and 16 weeks and thereafter about every 3-6 months. In general, many dogs need initial dose increases and later during long-term therapy, dose decreases.

3. Timing of monitoring

The treatment is monitored by regular ACTH-stimulation tests. The timing of post-pill sampling is most important. It is well known that post-ACTH cortisol varies depending on the interval between dosing and testing. Therefore, it is important to keep the interval constant for each patient from test to test. We perform the ACTH stimulation test 2-3 hours post-pill and use a reference range of 2-5 ug/dl (55-135 nmol/l) for the post-ACTH cortisol. The same treatment goals are used for dogs on twice daily therapy.

4. Efficacy

In the majority of patients trilostane is highly effective in suppressing cortisol secretion and controlling clinical signs. Many clinical signs (e.g. decreased activity, polyuria and polydipsia) resolve quickly, but certain ones (e.g. dermatological

abnormalities, pendulous abdomen) can take several months to improve.[2-4] A small proportion of dogs with pituitary-dependent HAC are not well controlled with trilostane.

In dogs with concurrent diabetes mellitus we prefer to start trilostane twice daily to more consistently decrease the cortisol levels. Insulin requirements and fructosamine concentrations do not consistently decrease during trilostane treatment.[5] Furthermore, prospective reduction in insulin doses at the start of trilostane treatment is probably not warranted.

Trilostane does work in adrenal-dependent HAC. Comparison of the median survival times between mitotane and trilostane treated dogs with adrenal-dependent HAC revealed no significant difference.[6] Although the studies have limitations and the numbers of dogs included were small, it seems that the use of mitotane in adrenal dependent HAC does not confer a major clinical advantage.

5. Safety

Adverse effects of trilostane are usually mild and self-limiting and most often include lethargy and vomiting.[2-4] Excess adrenal gland suppression, however, can occur and warrants immediate discontinuation of trilostane therapy. As trilostane is a competitive enzyme inhibitor, its effect should be rapidly reversible. However, in some cases adrenal suppression can last weeks to years. In these cases adrenal necrosis may be suspected, possibly induced by the elevated ACTH concentrations during therapy.[7,8] With oversuppression, we recommend discontinuing trilostane therapy, administering a few days of prednisolone if dogs show clinical signs of adrenal insufficiency and waiting with the re-starting trilostane therapy until the clinical signs of HAC return. Before re-start of trilostane therapy, we prefer to perform an ACTH stimulation test to document adrenal restoration. Trilostane should then be re-introduced at a very low dose (0.1-0.5 mg/kg) and increased very slowly.

Literature

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Anschrift des Verfassers

Nadja Sieber-Ruckstuhl

Klinik für Kleintiermedizin, Vetsuisse Fakultät, Universität Zürich

Winterthurerstr. 260, 8057 Zürich, Schweiz

nsieber@vetclinics.uzh.ch